Preface

All too often, developments in a field are so rapid that they outpace efforts of a reviewer to present a completely current picture. So it seems to have been with several of the topics presented in this volume. The relationship of von Willebrand's factor to antihemophilic factor (factor VIII) and the pathophysiology of the blood vessel are perhaps notable examples of this dilemma. The author of a chapter will view his galley proofs with some dismay as he perceives sections which would benefit greatly from updating, but the publishing facts-of-life severely restrict his ability to do so.

Fortunately, the function of a review is not to present a subject with the immediacy of a news broadcast. Rather, it is to provide perspective in an area that is suitably circumscribed. The reader can thus gain an enhanced background in this area, can apply that which is durable, and can use the background to better understand and assimilate current developments. Moreover, a skillful review can take a beginner by the hand and introduce him atraumatically into otherwise potentially hostile territory. The Editor hopes the readers of this book agree that its authors have accomplished such a mission.

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The Bleeding Time

INTRODUCTION

One of the most clear and dramatic descriptions of bleeding after skin puncture was given by Shylock in *The Merchant of Venice*, but in fact the phenomenon had been described about 3000 to 4000 years ago:

> When one punctures the region of the "sunlight," blood and air are issued forth; when one punctures the region of the great Yang, blood and noxious air are issued forth; when one punctures the region of the lesser Yang, air and foul blood are issued forth; when one punctures the region of the lesser Yin, air and blood are issued forth; when one punctures the region of the absolute Yin, blood and noxious air are issued forth.*

This quotation is an ancient description of acupuncture. It is probably one of the earliest descriptions of bleeding after pricking the skin, a procedure performed in ancient and in modern China for therapeutic rather than diagnostic reasons. In these ancient writings we were unable to find any description of the occurrence of prolonged bleeding after removal of the acupuncture needle, although prolonged bleeding has been reported in subsequent descriptions of bleeding-time tests.

In a paper written in 1951, O'Brien [71] defined the bleeding time as the time between the infliction of a small standard cut and the moment when the bleeding stops. O'Brien's definition is admirably clear and precise, and such a test appears simple in principle. However, there are many variables which affect such a test and they will be reviewed in some detail. First the anatomy of the skin must be considered so that the problems of standardizing the incision can be appreciated.

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* From *The Nei Ching, The Yellow Emperor's Classic of Internal Medicine*, Chapters 1–34, translated from the Chinese with an Introductory Study by Ilza Veith. Baltimore, Williams & Wilkins, 1949, p. 211.

ANATOMY OF THE SKIN

Histologically, the skin is composed of two main layers, a surface epithelium (the epidermis) and an underlying connective tissue layer (the dermis). Beneath the dermis is a layer of superficial fascia or fatty tissue which is connected to the deeper connective tissue structures such as the aponeuroses, periosteum, and deep fascia. The epidermis is made up of stratified squamous epithelium and has a horny exterior layer. It varies from 0.07 to 0.12 mm in thickness, although it is thicker on the palms (up to 0.8 mm) and the soles (1.4 mm). The skin has an intricate pattern of ridges between which fingerlike projections of the dermis (known as papillae) protrude into the epidermis. The epidermis thus varies in thickness depending on whether it overlies a papilla, where it will be thin, or is between papillae, where it will be thick. The papillae are largest on the hands and feet and smaller in other areas of the integument such as the forearm, where the bleeding time is often [illegible]sured. The thickness of the dermis is difficult to measure exactly because it [illegible]ds into the deeper layers. It is approximately 1 to 2 ml thick on most areas of the body with an increase of up to 3 mm on hands and feet.

The skin is supplied by blood vessels in the subcutaneous layer. The arteries in this layer form a network of branches in the lower levels of the dermis, parallel to the surface of the skin. This network provides a blood supply to the fat globules and sweat glands, and it sends off other branches to the papillary layer of the dermis where a second or subpapillary network is formed. This network sends branches into the papillae in the form of loops. The ascending arm of the loop is arterial and the descending is venous. The papillary loops drain into a network of veins below the papillae. From the subpapillary venous network the blood drains into two other venous networks at different levels of the dermis and finally into a large network in the subcutaneous tissue. When a bleeding time test is performed at a depth of 1 to 2 mm, the vessels incised would be mainly capillaries and small arterioles and venules from the capillary loops and subpapillary plexus.

BLEEDING-TIME METHODS

The first description of the bleeding-time test is usually credited to Duke [36], described his method in a paper presented at a meeting of the American cal Association in 1910. However, a bleeding-time test was described several years earlier than this in a paper presented by Milian [63, 64], at a meeting in Paris on July 5, 1901. Milian was studying the coagulation time of successive drops of blood from a finger prick. He found that the first and last drops of blood coagulated more rapidly than the majority of the intermediate drops of blood, and a drop obtained by pressure, after the hemorrhage had stopped, coagulated most rapidly of all. During the performance of this test he also recorded the duration of the hemorrhage (which, he noted, in a healthy subject was between 2 and 3 minutes), the total number of drops, and the number of drops per minute. His article therefore contains what is probably the first report of a prolonged bleeding time in the literature—a bleeding time of 9 minutes in a patient with cirrhosis of the liver. Another patient with von Recklinghausen's disease had a bleeding time of 4 minutes 40 seconds.

In a later article, Milian [62] described some modifications of his earlier method and published a graphic recording of his curves of hemorrhage and coagulation. It is interesting that the very first bleeding-time technique described attempted to give more information than any method described subsequently. Not only was the duration of bleeding measured but also the rate of bleeding and the coagulation time of the individual drops of blood were noted. The test is described as one of coagulation in the title of the original article, which probably accounts for the fact that Milian has not received recognition for his description of the bleeding-time test.

Methods Recording Only Duration of Bleeding

Method of Duke

At the time Duke [36] wrote his paper there were only about 20 cases of thrombocytopenia in the literature and there was considerable controversy as to the importance of platelets in hemostasis—indeed, there was controversy about the very existence of platelets. Duke showed that bleeding time in his patients was clearly related to the platelet count and not to the coagulation time. His method involved making a small cut in the lobe of the ear, but the instrument used and the depth of the cut were not reported. However, he did advise that the cut should be of such a size "that the first half-minute's outflow of blood makes a blot 1 or 2 cm in diameter" in the absorbent paper which is used to blot up the blood at half-minute intervals. He also provided evidence that, within certain limits, the duration of the hemorrhage should be independent of the size of the cut, and he gave the normal range for his test as between 1 and 3 minutes. Since the original description, the test has undergone many modifications.

Borchgrevink [13] thought that the size of the cut does not affect the duration of bleeding and recommended that a puncture 3 mm deep be made in the earlobe with a spring lancet or other sharp instrument.

In most techniques for the Duke bleeding-time test, a vertical incision is made in the lobe of the ear. Soulier (quoted by Blatrix and Corredor) [7] suggested using a horizontal incision on the lobe of the ear because this allows the bleeding to be more readily controlled by the application of pressure, an important point in the severe bleeder. Ratnoff [86] advocated incision of the ball of the finger rather than the ear because this would allow the bleeding to be more easily controlled. Quick [83] uses a cut 3 mm deep inflicted by a sterile spring lancet. He advocates holding the lobe of the ear taut and applying a slight but steady pressure to ensure the onset of bleeding.

Pauwen et al., [79] from their studies on rabbits, have devised a technique in which five incisions are made in each ear and the mean bleeding time is determined. The incisions are made with a sharp scalpel but the exact dimensions and depth were not given. These authors analyzed statistically 2,000 bleeding times done by two different observers on 100 men and 100 women. In another study they analyzed 400 mean bleeding times (that is, the mean of 5 bleeding times on one ear) done on both ears. They concluded that there was a systematic error involving the operator and were the first to show this important variable statistically. They also found a close correlation between the mean bleeding times in both ears.

Spitz [101] modified the Duke method by making a wound of fixed depth in the earlobe with a Francke blood lancet and, before measuring the bleeding time, rubbing the lobe firmly to ensure maximal flow of blood.

Van Dishoek and Jongkees [111] modified the Duke test to imitate as nearly as possible an open wound because the resistance to the blood flow from a stab wound would be enhanced by the edges of the wound adhering together. The earlobe was first made hyperemic by rubbing and then was pressed against a thin steel plate with a circular opening 4 mm in diameter. The part of the lobe protruding through the hole was cut off with a razor and the blood was absorbed every half minute on filter paper without the wound being touched. They made the observation that the method is less painful than a puncture. The average bleeding time in 450 tests on 85 subjects was 3 minutes 25 seconds (no range was given). These authors stated that the difference between duplicate determinations was more than 1 minute in only a few cases. One of the reasons for devising this test was that a small puncture wound [redacted] give a normal bleeding time in hemophilia and that their technique simulates [redacted] pen wound.

Aspirin Tolerance Test of Quick

The work of a number of investigators has established that aspirin ingestion prolongs the bleeding time. Quick [82] reported that in a series of normal medical school and college students more than half had a small but significant prolongation of the Duke bleeding time 2 hours after ingestion of 1.3 gm of aspirin. Many patients with mild von Willebrand's disease have bleeding times which vary in duration and are sometimes normal. Quick found that these patients were more sensitive to aspirin and showed a significantly prolonged Duke bleeding time 2 hours after the ingestion of only 0.65 gm of aspirin. This is the basis of the aspirin tolerance test, which he thinks is helpful in the detection of patients with mild von Willebrand's disease.

Method of Ivy

In an investigation of the bleeding time in jaundice, Ivy and co-workers [51] found that the bleeding time was very often normal. They thought that the state of "tonicity" of the capillaries was a variable in the bleeding time by the Duke method [redacted] that a latent bleeding tendency might be revealed if the factor of capillary tonus [redacted] be eliminated and the capillaries kept wide open. They therefore increased the [redacted] ssure in the capillaries by inflating a blood-pressure cuff around the upper arm to a pressure of 40 mm Hg in order to occlude the venous return. The skin of the forearm near the elbow, over the pronator muscles, was selected as the site of testing because the skin in this area was uniformly thin without differences in "hornification." Punctures were made with a mechanical stylet set to a uniform depth of about 2.5 mm. A total of 115 normal subjects was studied and, although the new method gave somewhat longer bleeding times and an increased volume of bleeding (as demonstrated by the area of the drops of blood on the filter paper), there was very little difference between the results of the Duke method and this method. The upper limit of normal was fixed at 240 seconds but normal values were rarely over 180 seconds.

The Ivy method was later modified [50] by using a Sharpe and Smith lancet and increasing the depth of the blade setting to 3 mm because at the lesser setting some of the incisions failed to bleed. An attempt was made to control the pressure placed on the lancet in order to standardize the depth of the puncture. The weight of the lancet was adjusted so that in most subjects it depressed the skin approximately 1 cm. In thin muscular subjects, more pressure had to be applied to achieve a depression of 1 cm, resulting in unduly long bleeding times. The authors concluded that neither the application of the same amount of pressure nor the identical depression of the peripheral tissues was able to ensure punctures of equal depth. They thought that adjusting the pressure or depression of the skin did not significantly affect the reproducibility of the test.

A study of the reliability of the technique was made in 88 normal persons; five pairs of punctures of the skin were made in each subject, the second puncture being made 5 seconds after the first puncture and not less than 2.5 cm away. The maximal normal bleeding time of 240 seconds was confirmed. The mean (± SE) bleeding time was 61.56 ± 2.08 seconds. There was no sex difference. In 31 subjects who were retested there was no significant variation in the mean bleeding time. Statistical analysis showed that the second puncture of each pair bled significantly longer than the first, and that the mean bleeding time of the last five punctures was significantly greater than that of the first five.

Tocantins [110] described a modification in which he used a 12-blade scarificator from which all but 1 of the blades were removed. When the spring on the scarificator was released, the blade followed a central circular track as it cut rapidly and painlessly into the skin. The depth of the cut could be adjusted, but no mention of the depth used was made in the paper.

O'Brien [70, 71] made three incisions in the forearm with a spring lancet and slid a piece of filter paper lightly over the wound every 15 seconds. The mean bleeding time in his series was 5.7 minutes (5.0 for males and 6.5 for females). The range was 0 to 15 minutes, but by expressing the times logarithmically he found that the values fitted a curve of normal distribution.

We also have developed a spring-loaded lancet [77] which makes a puncture in the skin by means of a disposable scalpel blade. The depth of the puncture can be varied, and the lancet automatically retracts the blade.

Hjort and Stormorken [46] modified the test by making cuts in the skin instead of using the stylet. They made two cuts, 2 to 3 mm long, 0.5 to 1 mm deep, and 2 cm apart with a Gillette surgical blade (shape E). The average value was taken as the bleeding time. The timing was stopped when the blot on the filter paper no longer had a reddish tinge. In many persons a serous discharge continued but was not included in the bleeding time. In 35 tests in 13 normal persons the mean bleeding time was 6.2 minute (range, 2 to 12.5 minute).

Mielke and colleagues [61] standardized the Ivy bleeding-time method by using a template system to obtain an incision of standardized length and depth. The technique described by these authors is extremely reproducible. A No. 11 Bard-Parker blade is attached to a polystryrene block by means of screws and its protrusion from this handle is adjusted by means of a gauge. The polystyrene template (5.5 cm long × 2.5 cm wide × 1.5 cm thick) contains a central slit 11 mm long × 1 mm wide; when the blade secured in the handle is placed through the slit, an incision will be made which is 9 mm long × 1 mm deep. The sphygmomanometer cuff is inflated to 40 mm Hg. Thirty seconds later the template is placed on the forearm 5 cm from the antecubital fossa, with the longitudinal slit parallel to the antecubital crease.

The template is pressed against the skin firmly to flatten the surface of the skin. The blade is introduced at right angles at one end of the slit and three incisions are made along the length of the slit, 1.5 cm apart. These incisions are blotted with Whatman No. 1 filter paper strips every 30 seconds. Care is taken to avoid touching the wound edges. The mean of the individual times is the bleeding time. The subject should be advised that there is a rare possibility that a keloid will form. The mean bleeding time of 60 normal subjects was 5 minutes and the range was 2 minutes 30 seconds to 10 minutes.

Secondary Bleeding Time

The basis for the development of the secondary bleeding time, by Borchgrevink and Waaler [10, 14], was the tendency of patients with coagulation factor deficiencies to ooze after trauma or to bleed again after hemorrhage had stopped, despite the fact that their bleeding time was normal. The Ivy technique was [illegible]ed by making cuts with a surgical blade (Gillette, type C. B.) about 10 mm [illegible]x 1 mm deep. In the original method, cuts of two lengths were made—3 to 4 mm and 12 to 14 mm. The longer cuts were recommended because there was less overlapping between the primary and secondary bleeding times than with the shorter cuts. Twenty-four hours after the cuts were made, renewed bleeding was provoked by gently removing the crust with a surgical blade. Care was taken to avoid causing new tissue damage or cutting new vessels. In normal subjects, the secondary bleeding time was always shorter than the primary bleeding time. In patients with intrinsic blood-clotting factor defects, the secondary bleeding time was prolonged. The test is of physiologic interest but has limited clinical value.

Immersion Methods

To eliminate the variable of skin temperature, bleeding-time methods have been devised in which the incised skin is immersed in a bath of saline kept at a constant temperature.

Method of Copley and Lalich [20]

A "hemorrhagometer" was constructed which consisted of a constant-temperature bath capable of maintaining 200 ml of isotonic saline at 37.5°C. After [illegible]rminal phalanx of the third or fourth finger was cleaned with alcohol, it was [illegible]ersed for 2 minutes in the bath and then a wound 6 mm in depth was produced with a mechanical stylet (blade dimensions 0.5 × 2 × 6 mm). Wounds less than this depth often failed to produce a free flow of blood. The hand was kept at a level of 10–15 cm below the base of the heart to keep the venous pressure constant. The bleeding time was measured until the flow of blood stopped. It was noted that a whitish flow often continued and the time of its cessation was referred to as "lymph time," but its significance could not be evaluated.

The authors made 334 determinations of bleeding time in 174 subjects. The range was 17 to 340 seconds, 95 percent of the values falling between 17 and 118 seconds. The authors regarded 6 minutes as a pathologic value. There was a latent period before the onset of bleeding, which ranged up to 4 seconds. In duplicate tests done within an hour, 104 of the 105 comparisons agreed within ± 30 sec. Some of the blood flow from the wound was noted to be pulsating, but in these subjects the bleeding time was not appreciably longer than when flow was nonpulsating.

A water bath temperature less than 36.4°C prolonged the bleeding time, but there was no significant difference between the bleeding time at 50°C and at 37.5°C.

Method of Adelson and Crosby [2]

The hand was immersed to the wrist for 3 minutes in a large beaker containing isotonic saline at 37°C. During this time a sphygmomanometer cuff was applied to the upper arm and inflated to 40 mm Hg. After 3 minutes the hand was removed from the saline, dried with gauze, and treated antiseptically. Then a stab wound was made in the hypothenar eminence with a No. 11 Bard-Parker blade protruding from a cork stopper to a distance of 4 mm. The hand was replaced in the warm saline and the bleeding time was recorded. The blood loss was also measured. The blood loss was calculated by measuring the hemoglobin concentration in the saline in the beaker (after lysing the erythroctyes with saponin) and the hemoglobin concentration of the subject's whole blood. In 27 controls the upper limit of normal was 7 minutes, the doubtful range was 7 to 8.5 minutes, and the abnormal range was above 8.5 minutes. Less than 0.22 ml was normal blood loss, 0.22 to 0.3 was doubtful, and above 0.3 ml was abnormal.

Method of Macfarlane

This was mentioned by O'Brien [71]. An incision is made in the earlobe which is then immersed in saline.

Methods for Quantitating Blood Loss and Bleeding Times

Although earlier workers had made attempts to estimate blood loss semiquantitatively, the immersion method of Adelson and Crosby was the first attempt to measure blood loss accurately. In most other methods the only observation made was duration of bleeding. However, other details may be worth recording, including the time between the puncture of the skin and the start of bleeding, the time at which the bleeding becomes maximal, and the total amount of blood lost. From visual inspection it is apparent that some patients bleed profusely although the duration of bleeding is normal. In some subjects the bleeding starts immediately and in others it increases gradually. Sometimes rebleeding occurs. In von Willebrand's disease the amount of blood lost from the wound often appears to lessen after transfusion although the bleeding time may not be shortened. It is surprising therefore that few investigators have attempted to measure the amount of blood lost from the wound and to record the pattern of bleeding.

Willoughby and Allington [115] measured blood loss by eluting the blood from the filter paper used to blot the skin puncture. The filter paper was placed in 50 ml of 0.04 percent ammoniated distilled water and agitated for 30 minutes; then the hemoglobin in the supernatant solution was estimated. The Ivy bleeding time technique was used and a puncture was made with a spring lancet set to a depth of 3 mm. The wound was blotted every 15 seconds with Whatman No. 1 filter paper. The mean from three punctures was taken as the bleeding time and in normal subjects it was 3.6 minutes (range, 1.5 to 7.2 minutes). The mean rate of blood loss was 6.8 mm^3/min (range 1.4 to 13 mm^3/min). The authors mentioned that in repeated tests on a specific subject the range was less. Fifteen of the patients studied had normal bleeding times but an increased rate of blood loss, and the majority of the pa-

tients had hemorrhagic symptoms which required further investigation. High blood loss was noted in von Willebrand's disease, thrombocytopenia, capillary bleeding, and renal failure. Low volumes and rates of blood loss were found in hemophilia, Christmas disease, and patients on Dindevan therapy. Borchgrevink [12] also measured blood loss by eluting the blood from the filter paper.

De Nicola [27] and de Nicola and Candura [28] modified the Duke test and quantitated the blood loss by collecting the drops of blood from the patient's ear into a glass capillary tube, 1 mm in diameter and 90 mm long, at intervals of 30 seconds. If the bleeding was intense the blood was collected every 15 seconds. The heights of the column were plotted in sequence to reflect the variations of bleeding intensity and bleeding time. De Nicola [27] reported increased bleeding intensity but normal bleeding times in patients with cirrhosis of the liver and hypertension.

Sutor and co-workers [17, 104, 107] described a method for the continuous automated recording of blood loss during the determination of the bleeding time by modification of the Ivy technique. The patient reclines on a couch and the skin of the forearm is cleaned with 70 percent ethanol and dried. A sphygmomanometer cuff on the upper arm is inflated to 40 mm Hg and carefully maintained at this pressure throughout the test. A standardized incision is made transversely in the skin of the forearm with a No. 11 Bard-Parker blade in the Mayo automatic lancet. The lancet is set to give an incision 5 mm deep; when it is allowed to rest on the skin by its own weight, the actual depth of incision is between 1 and 2 mm. A transparent Lucite cube (sterile) is placed over the incision, and sterile distilled water at 25°C is sucked through the flow cube by an AutoAnalyzer proportioning pump. In this way the blood is diluted and hemolyzed. The slightly negative pressure from the proportioning pump holds the flow cube to the skin. The stream of water is interrupted at regular intervals by bubbles of air to prevent tailing of the blood. The hemolysate is passed through a system of coiled glass tubes for mixing for 6 minutes and then is debubbled before it is passed through the flow cell of a spectrophotometer. Absorbance is measured at 542 nanometers (or 410 nm if the concentration of hemoglobin is low) and recorded continuously on a chart recorder.

Bowie et al. [16] described a modification of the technique in which the hemolyzed blood is passed through a conductance transducer instead of a spectrophotometer. The device is calibrated on a sample of the patient's own blood at a specified dilution and the conductivity is recorded continuously on a strip chart recorder. The area under the curve is integrated electronically and the volume of blood is indicated on a meter.

Three patterns of bleeding were found. The pressure in the blood pressure cuff had a significant effect on the amount of blood loss. Longitudinal and transverse incisions were compared and, although the bleeding time was not significantly different, a greater amount of hemoglobin was lost from longitudinal incisions than from transverse ones. When the skin incision was 0.8 to 1.2 mm deep, the mean bleeding time by the spectrophotometric method was 191 seconds (range, 100 to 260 seconds; SD, 48 seconds; 31 tests on 22 normal persons). The mean blood loss was 0.76 mg of hemoglobin (range 0.25 to 1.4 mg; SD, 0.39 mg). With the electronic technique, the mean bleeding time in 26 normal adults was 360 seconds with a blood loss of 5.3 μl.

The determination of blood loss has been helpful in diagnosis and in following therapy in patients who have normal bleeding time but who show an increased loss of blood. In most patients with congenital coagulation factor deficiencies, the blood loss during the bleeding-time test is normal.

Bleeding-Time Methods in Animals

Duke Method and Modifications

The method described by Duke has been widely used in animals, and in most domestic animals the bleeding time by this technique varies between 1 and 5 minutes [33]. The rabbit's ear offers the experimenter a target to skewer that is mind-boggling in the vastness of its puncturable area; however, the bleeding time varies in different parts of the ear [92]. In the technqiue described by Roskam and Pauwen [92], the anterior surface of the ear is shaved and an incision is made halfway through the thickness of the ear for a distance of several millimeters. An area is chosen which allows easy observation of the collateral vessels. The incision is gently bathed with a weak stream of liquid maintained at a constant temperature. The liquid may be water, physiologic saline, or some solution being tested for its effect on hemostasis. The authors think that the liquid medium reproduces, "albeit imperfectly," the conditions in which bleeding occurs in vivo. Because they have found that the bleeding time varies in different regions of the ear, they make five incisions in four different areas—a total of 20 in all—and average the results to calculate the mean bleeding time.

The Duke technique has also been applied to chickens by making a uniform incision on the comb with a disposable blood lancet; in 25 mature chickens the mean bleeding time was 480 seconds (range, 120 to 690 seconds) [6].

Mertz [60] described an immersion method for measuring the bleeding time in a herd of swine that subsequently were found to have von Willebrand's disease. The ear is shaved and a lancet wound is made near the edge to a depth similar to that in the Duke method (the paper states the depth to be 1 to 2 cm but presumably 1 to 2 mm is meant). The ear is then immersed in 0.9 percent saline at 37°C in a 1-liter beaker and timing is continued until the bleeding has stopped.

Techniques Using a Tail of Rat or Mouse

Copley and Lalich [19] modified a method first described by Döttl and Ripke [35] in which the bleeding time is determined on the tail of a mouse. The mouse is placed in a brass tube 7.5 cm long, a perforated cork occludes the tube at the head, and the tail is passed through a Lucite tail holder and immersed in a physiologic saline bath at a constant temperature of 37.5° C. A cut is made in one of the tail veins with a stylet with a needle point. The bleeding time is measured from the moment the blood is seen coming from the wound until cessation of flow. In 310 determinations in 118 normal mice, the mean was 54 seconds (range 15.4 to 220 seconds).

A method using the rat tail was devised by Cruz [21]. A small area of keratinized epidermis in the rat tail is removed with a razor blade. The bleeding stops in 1 to 2 minutes. The area is then scoured with a piece of gauze and immersed, in a vertical position, in a beaker containing physiologic saline at a temperature of 37°C. In 117 observations the bleeding time averaged 67 seconds (range 20 to 138 seconds; SD, 22 seconds). The bleeding can be observed through a

dissecting microscope at a magnification of 30 to 50 times so that individual vessels can be seen.

Miscellaneous Methods

The dog's hind-limb preparation has been used by Cruz and Oliveira [24] for the study of hemostasis. Blood treated in various ways can be used to infuse the limb, and hemostasis is measured by performing a bleeding-time test. The medial side of the thigh is carefully shaved and two superficial cuts, each 5 to 10 mm long, are made with a safety razor through the thickness of the epidermis but not into the subcutaneous layer. The cuts are made far apart and parallel to the length of the thigh. At specific intervals, blood oozing from the wound is collected for 1 minute on a small piece of filter paper of known weight and these are weighed again to determine the amount of blood that had been lost in the measured interval. In this [illegible]he rate of bleeding was determined.

[illegible]he bleeding time can be determined by direct microscopic observation of incised cutaneous vessels in anesthetized animals [49]. Dodds and Kaneko [33] considered this to be the most accurate method of performing the bleeding time test in animals. The subcutaneous and fascial vessels are exposed by an incision 1 to 3 cm long on the medial side of the thigh. The area is illuminated by means of a quartz rod and the vessels are then transected with a razor blade. The wound is bathed in Tyrode's solution at 30 to 37°C by means of a slow drip. A similar technique can be used to observe bleeding from mesenteric vessels.

STANDARDIZATION OF BLEEDING-TIME TEST

The various tests of the bleeding time have the reputation of giving variable results and thus being not very helpful in the diagnosis of hemostatic defects. In actual fact, the bleeding-time test will give reliable, reproducible results if the variables are carefully standardized and if the test is meticulously performed by an experienced operator. Many conflicting statements have been made about the significance of the bleeding time. Some think that a marked prolongation of the bleeding time indicates an abnormality of hemostasis, and others have stated that a [illegible] bleeding time is not compatible with a significant platelet or capillary [illegible] In our experience neither statement is true.

Although it is extremely difficult to prolong the Ivy bleeding time artifactually, the Duke bleeding time can easily be prolonged by squeezing the lobe of the ear. Furthermore, it is not uncommon to see patients with mild von Willebrand's disease who have normal bleeding times. Many of these conflicting statements are the result of differences in techniques for the performance of the test, but more specifically are the result of inadequate attention to standardization of the variables which may affect the test. These factors will now be considered in detail.

Site of Skin Puncture

Because the thickness of the skin varies from one area of the body to another and from one individual to another, the depth of penetration into the vascular subcutaneous tissue will vary even when the lancet is set for a fixed depth. One of the reasons that Duke chose the earlobe and Ivy the upper part of the forearm is that the skin in these areas varies little from individual to individual.

Vascularity

It is important to choose an area that is free from large blood vessels so that only small blood vessels are severed by the incision. In Quick's opinion [84], the ear is a particularly appropriate site because as it has no motor function, it has only a small blood supply, and consequently the tissue contains only minute vessels. In most descriptions of the technique it is recommended that the site be cleaned as gently as possible so as not to induce hyperemia. On the other hand, Szécsi [108] and van Dishoek and Jongkees [111] advised that the area be rubbed before the cut is made. Quick [83] thought that such a maneuver could introduce serious error in the bleeding time.

Venous Pressure

Ivy et al. [51] noted that when capillary pressure was increased by inflating a sphygmomanometer cuff around the upper arm to a pressure of 40 mm Hg, the bleeding time was somewhat longer, and there was an increased volume of bleeding as demonstrated by the total area of the drops of the blood on the filter paper. Although most authors advocate that the pressure be carefully maintained throughout the performance of the test, there are few data in the literature about the effect of varying the pressure in the sphygmomanometer cuff. By our quantitative technique we have been able to demonstrate that the intensity of bleeding is clearly related to the pressure in the cuff on the upper arm [107].

Size and Depth of Puncture

In his original article, Duke gave evidence that within certain limits the duration of bleeding did not depend on the size of the incision. This observation has subsequently been challenged, particularly for estimations of small deviations from normal [13]. When the bleeding time was measured by the Ivy technique, we found that increasing the depth of the cut increased the duration and the amount of bleeding [107], and Borchgrevink and Waaler [14] reported that increasing the length of the incision prolonged the bleeding time slightly but significantly. It would seem advisable therefore to attempt to standardize the length and depth of the incision. Such as undertaking presents many problems.

The main difficulty is that the epidermis and dermis are compliant, and there is compression of the dermal layers by the cutting instrument. This applies not only when an incision is made manually with a scalpel but also when pressure is exerted by a spring-loaded lancet. Ivy was the first to attempt to control these variables by weighting the lancet so that it would indent the skin to a depth of 1 cm in most subjects. In some subjects more pressure had to be applied to achieve the desired depression of the skin, and in these instances a deeper incision was made. We allow our lancet to rest on the skin by its own weight (81 gm, producing a pressure of 43.3 gm/cm^2). When the blade extends 5 mm from the holder, the mean depth of the wound is 1 mm. A deeper wound would be produced of course if the lancet were

pressed firmly against the skin. So far, no foolproof way has been found of making a standardized incision in the skin, and the reproducibility of all the techniques depends on the expertise of the operator.

Few workers have studied the effect of the direction of the incision on the duration of bleeding. Nilsson and colleagues [69] found no difference in the bleeding times between transverse and longitudinal incisions using the Ivy technique.We [107] quantitated the duration and amount of bleeding from longitudinal and transverse incisions in the forearm, using our quantitative technique. Nineteen tests were performed on 16 normal persons and, although there was no significant difference between the bleeding times, the quantity of blood lost was significantly higher after the longitudinal incisions than after the transverse incisions. The pattern of bleeding also was different, a rapid onset of intense bleeding being more common after longitudinal incisions whereas the onset of bleeding was nearly always gradual from a transverse incision.

Temperature of Skin

Since the time of Hippocrates [53, 102], it has been thought that cold hastens hemostasis, and most textbooks advocate the application of cold for this purpose. For over 40 years, however, studies on the effect of temperature on bleeding have suggested that cold, if anything, makes bleeding worse [55, 88, 108]. Quick [83] showed clearly that chilling of the earlobe causes a significant prolongation of the bleeding time by the Duke method. In other studies, fingers of humans [91] or tails of mice [19] or rats [21] were immersed in saline at different temperatures. Bleeding times were significantly prolonged at low temperatures. In one report [19], the bleeding time was prolonged in temperatures below 37.5°C.

When we used our quantitative technique and cooled the water flowing over the wound to 16°C, there was a significant increase in the duration and amount of bleeding in all normal persons [103]. In patients with coagulation factor deficiencies, the bleeding time became indefinite and continued until the test was terminated. There was no significant difference in the duration or amount of bleeding between 33°C and 25°C. The technique we described is different from the other experiments that have been reported in that only the area of the wound is cooled, the surrounding skin remains at physiologic temperature. It is possible that this technique can be used as a cold tolerance test to detect patients with mild disorders of hemostasis in which other tests are not significantly altered.

It is of interest that, in von Willebrand's disease, cool water caused a slight decrease in the intensity of bleeding. The explanation for this has not been investigated experimentally, but it seems possible that the effect is due to vasoconstriction in a patient who is already bleeding maximally.

Effect of pH

The first studies of the effect of pH on the bleeding time were made by Roskam [89] who undertook the investigation because acidic preparations were often used for their hemostatic effect. He found that when water adjusted to pH 5 with hydrochloric acid was used to bathe the incision, the bleeding time was shortened, but when the pH was increased to 9.2 with sodium hydroxide the bleeding time was prolonged. These results are in direct conflict with observations by Cruz [21], who studied bleeding from rat tails and found that acetate or succinate buffer at pH 5.4–4.5 had an inhibitory effect on hemostasis.

EFFECT OF MEDICAMENTS AND OTHER SUBSTANCES ON BLEEDING TIME

Studies of the effect of drugs on the bleeding time have been sporadic and have been devoted mainly to those drugs thought to have a vasoactive or hemostatic effect. The first reported studies were published by Weil [112] in 1921, who noted that epinephrine administered intravenously or subcutaneously caused smaller drops to appear from the incision (Duke method), whereas amyl nitrite increased the size of drops although neither drug affected the bleeding time. Posterior pituitary extract and emetine, on the other hand, decreased the size of the drops and also shortened the bleeding time.

Vasoconstrictor substances and drugs shortening the coagulation time have been tested by a number of workers, at first in animal experiments and subsequently in humans. In a study in rabbits in 1934, Roskam [90] measured the effect of a number of substances by bathing the wound with them, injecting them around the wound, or injecting them subcutaneously, intramuscularly, or intravenously "into the circulatory torrent." The substances tested included calcium salts, peptone, gelatin, an extract of lung, and a derivative from the serum of sensitized animals. Many of these substances were found to prolong the mean bleeding time. Adrenochrome, an oxidation product of epinephrine, and some stable compounds derived from it were shown to shorten the bleeding time [91].

Derouaux tested a number of intriguing substances in rabbits and found that an extract of spinal cord prolonged the bleeding time [29], toad venom had no effect [30], and thrombin produced shortening [32]. He also obtained shortening of the bleeding time with adrenochrome, adrenochrome monoxime, and adrenochrome monosemicarbazone [31].

Blood, Plasma, and Cephalin

Cruz and Oliveira [24] used a bleeding-time technique in studies of the effect of various substances on hemostasis. They made incisions with a razor in the perfused hind limb of a dog and measured the time required for bleeding to stop. When the limb was perfused with blood anticoagulated with citrate or heparin or from which the platelets had been removed, there was no prolongation of the bleeding time. Denervation of the limb or death of the animal caused the bleeding to be prolonged to over 30 minutes [24]. In contrast to arterial blood, venous blood was unable to support hemostasis and actually inhibited the hemostatic properties of arterial blood [25]. The hemostatic effect of venous blood was restored by the addition of crude cephalin [26], Cohn fraction I-III, and Cohn fraction II taken from arterial blood [23]. Crude cephalin from ox and dog brain was fractionated according to the Folch method, and fraction V had a hemostatic effect although fractions I and III were inactive [22].

Substances Affecting Platelet Aggregation

Many studies on the effect of drugs on the bleeding time have been carried out by O'Brien. He injected the drug intradermally to make a bleb 10 mm wide and then made the bleeding-time incision across the bleb. He tested many drugs which inhibit the adhesion of platelets, including quinidine derivatives, antimalarials, local anesthetics, and antihistamines. Quinine, diphenhydramine (Benadryl), and cocaine, for example, caused marked prolongation of the bleeding time [75], although procaine and chlorcyclizine had no effect. O'Brien [72] pointed out that many of the drugs that prevent adhesion of platelets carry a positive charge, have a lipophilic hydrocarbon moiety, and have great pharmacologic activity.

In this study [74] on the effect of epinephrine and anti-epinephrine compounds on hemostasis, O'Brien found that phentolamine, which inhibits epinephrine and [illegible]epinephrine, prolongs the bleeding time. Although phentolamine produced a [illegible]r effect, manifested by erythema and local edema, O'Brien thought that its [illegible]effect was largely on the platelet because histamine and hyaluronidase caused erythema but not prolongation of the bleeding time. In another study [73], an antiserotonin drug, RO-3-0837, was given by mouth for several days, and the bleeding time was measured by a modification of the Borchgrevink method. In nearly all of the 7 subjects studied, there was an increase in the mean bleeding time during treatment. The amount of blood lost, indicated by the area of the largest blot, also showed an increase during treatment with this drug.

A modified Borchgrevink technique also was used to test the effect of substances which inhibit the aggregation of platelets by adenosine diphosphate [98]. Two cuts were made on the forearm; the control wound was flushed with buffered saline and the other wound, with solutions of the inhibitors. Prolongation of the bleeding time was produced by monoiodoacetate, iodine, *p*-chloromercuribenzoate, cysteine, and adenosine monophosphate.

Several hours after the intravenous infusion of 1 liter of 6 percent high-molecular-weight dextran solution, the bleeding time of normal persons often became prolonged [38, 57]. It appears that the prolongation of the bleeding time by dextran is the result of its platelet coating action [81, 93, 94], which also results in dimished platelet factor 3 activity [38].

spirin

In recent years, aspirin is the drug that has been most extensively investigated regarding its effect on the hemostatic mechanism. The story, which is by no means finished, is an example of how astute clinical observations can lead to the discovery of basic physiologic and pathologic mechanisms. For many years, Quick had suspected that aspirin caused hemophiliacs to have more difficulty with bleeding. Although Beaumont and his colleagues [4] and Frick [39] had observed that aspirin prolongs the bleeding time, and other workers have made similar observations, their findings had been overlooked until Quick's recent paper [82] on the subject stimulated further investigation. Quick studied a group of normal subjects and showed that half of them had a small but significant increase of the Duke bleeding time 2 hours after ingestion of 0.65 gm of aspirin. Sodium salicylate alone had no effect.

Quick suggested that aspirin prolonged the bleeding time by depressing a plasmatic factor which controls bleeding from small vessels. He further suggested that the action on this factor was determined by the acetyl moiety and not by the salicylate.

Investigation of platelet aggregation has shown that 2 hours after the ingestion of 1.2 gm of aspirin the secondary phase of platelet aggregation is completely inhibited together with the release reaction which includes release of endogenous ADP [76, 114, 116]. The ability of collagen particles to induce platelet aggregation is also inhibited. When aspirin was added in vitro, similar results were found [37]. Secondary platelet aggregation induced by epinephrine also is inhibited, as well as aggregation by antigen-antibody complexes [42], γ-globulin-coated surfaces, and triethyl tin [76]. Chlorpromazine, desmethylimipramine, and several drugs showing one or more of the properties of aspirin also inhibit the second phase of ADP aggregation. Sulfinpyrazone and phenylbutazone block the aggregating action of collagen, antigen-antibody complexes, and γ-globulin-coated surfaces but not that of ADP and thrombin. It has been suggested that aspirin affects some enzyme property in the platelet, and it has been reported [34] that aspirin inhibits platelet glycolysis. It recently has been proposed that aspirin's effect on the platelets is mediated by cyclic AMP and depression of the release of prostaglandins [99].

Although the aspirin-induced prolongation of the bleeding time may be due to an effect on the blood vessel, it seems more likely that it is due to the effect on the platelet [61]. Using their standardized Ivy bleeding-time technique, Mielke and colleagues [61] studied the effect of aspirin on 60 normal men. A control bleeding time was taken and then the subjects were given, on a double-blind basis, either 1 gm of aspirin or a placebo. A second bleeding time was determined 2 hours later. The control values gave a mean of 5 minutes (range 2.5 to 10 minutes). The values after the placebo were not significantly different but after aspirin the mean was 9.5 minutes (range 4 to 21 minutes). The study was meticulously performed and clearly demonstrated that aspirin prolongs the bleeding time in normal persons. The authors also noted that the drops of blood exuding from the wound were larger in some subjects after the ingestion of aspirin.

Sutor et al. [105] studied the effect of aspirin, sodium salicylate, and acetaminophen on bleeding time, using their quantitative technqiue, and recorded the pattern of bleeding. Sodium salicylate and acetaminophen did not alter hemostasis in the majority of normal subjects. All 15 subjects showed an increase in bleeding time 70 minutes after ingestion of aspirin. In 7 the bleeding time was prolonged by more than 2 minutes. In 12 of the 15 subjects the bleeding intensity was significantly increased; they lost at least four times as much blood as during the control period. The test was repeated after 24 hours in 3 subjects and after 4 days in one subject, and in all cases the abnormality was still present.

Anticoagulants

Patients on oral anticoagulant therapy have normal bleeding times [11] although it is stated that, during a hemorrhagic episode, the bleeding time may be prolonged [109]. Large doses of heparin may prolong the bleeding time in man, rats, and mice [47].

CLINICAL CONDITIONS ASSOCIATED WITH PROLONGATION OF BLEEDING TIME

Prolongation of the bleeding time usually results from defective hemostasis due to abnormalities of the capillaries or platelets. As Duke [36] pointed out, the bleeding time is normal in hemophilia. It also is normal in most other abnormalities of the coagulation mechanism with the exception of hypofibrinogenemia and some cases of factor V deficiency.

Disorders of Capillaries

In most of the diseases which involve the capillaries, such as scurvy, anaphylactoid purpura, drug purpura, infectious purpura, meningococcemia, streptococcal infections, epidemic hemorrhagic fever, and Schamberg's progressive pigmentary dermatosis the bleeding-time tests nearly always give normal results. This is also of the types of purpura which probably result from lax subcutaneous tissue and poor blood vessel support, such as senile purpura and Cushing's syndrome. It is interesting that, although the bleeding time is normal, in many of these conditions the tests for capillary fragility and resistance give abnormal results. It has been reported [84] that the bleeding time is prolonged in an occasional case of hereditary hemorrhagic telangiectasia. Although some of these patients may have prolonged bleeding times as the result of aspirin ingestion, apparently this is not necessarily always the case.

Quantitative Abnormalities of Platelets

In his original article, Duke [36] clearly showed that patients with thrombocytopenia had prolongation of the bleeding time, and that this was reversed when the platelet count was restored to normal levels. The thrombocytopenic patients he described are of interest in that the platelet count responded promptly to transfusions of whole blood; this is similar to the case reported by Schulman et al. [95] in which the patient seemed to lack a plasmatic thrombopoietic factor.

It is often stated that it is superfluous to perform a bleeding-time test in patients with thrombocytopenia. However, if the bleeding time in these patients is normal, it can be assumed that platelets and capillaries function adequately to support hemostasis in small wounds, whereas a prolonged bleeding time indicates that the hemostatic mechanism is decompensated.

The most interesting studies in this area have been reported recently by Harker and Slichter [44]. These workers found a linear relationship between the bleeding time (Mielke template method) and the platelet count. The mean normal bleeding time was 4.5 $\pm$ 1.5 minutes and, at a platelet count of 10,000/mm^3, the bleeding time was 25 minutes. Patients with thrombocytopenia due to splenic pooling or inherited thrombocytopenia had bleeding times which were consistent with the platelet count. In patients with idiopathic thrombocytopenic purpura, the bleeding time was much shorter than would be predicted from the platelet count. Patients whose platelet counts were increasing after chemotherapeutic bone marrow suppression also had unexpectedly shorter bleeding times. The authors suggested that the young platelets in patients with idiopathic thrombocytopenic purpura and following bone marrow suppression therapy have increased hemostatic competence. Young platelets also

were found to correct the bleeding time more effectively in a study of a patient with thrombocytopenia due to thrombopoeitin deficiency [52].

The bleeding time may be prolonged in patients with thrombocythemia as the result of a myeloproliferative disorder. Abnormalities of platelet aggregation, particularly with epinephrine, have been documented in these patients [67, 100].

Qualitative Platelet Diseases

The field of the qualitative platelet diseases is still developing and it is difficult at the moment to classify them in any reasonable way. The term "qualitative platelet disease" refers to defective function of the platelet, and in general these patients have normal platelet counts, although abnormal platelet function has been reported in patients with thrombocytopenia [93]. Some of the congenital platelet abnormalities which have been described have been associated with a prolonged bleeding time. These include Glanzmann's thrombasthenia [40], the Bernard-Soulier syndrome [5] (in which the platelets are large), a disease in which the storage pool of adenine nucleotides is deficient [48], and a prolonged disease in which the adenine nucleotides are not released from the platelet [65]. A bleeding time, decreased platelet factor 3 availability, and decreased platelet adhesiveness have been described in patients with glycogen storage disease [43].

A newer disease, described as "gray platelet syndrome" [85], in which there is a paucity of platelet granules with decreased ATP and phosphatides, is also associated with a long bleeding time. Functional abnormalities of platelets also have been described as associated with systemic disease such as liver disease, uremia, scurvy, and the dysproteinemias. In macroglobulinemia the platelet is coated with macroglobulin, which impairs the release mechanism.

In certain congenital and acquired conditions, platelet factor 3 is decreased either because the platelet has a deficient content of it or it cannot be made available in adequate amounts. Since the publication of the paper by Braunsteiner[18], the term "thrombopathy" has often been used to denote these abnormalities. Defective platelet factor 3 availability may be associated with aggregation abnormalities—for example, in Glanzmann's thrombasthenia—and the question as to whether it occurs as an isolated entity has not been completely settled. However, we have seen 2 patients with defective activation of platelet factor 3 in whom aggregation with ADP and collagen were normal (other aggregating agents were not tested). It is of interest that in both of these patients the bleeding time was normal, suggesting that the capacity of the platelets to aggregate and to adhere to collagen was unaffected.

Von Willebrand's Disease

Prolongation of the bleeding time was the first abnormality described in von Willebrand's disease, and it is certainly one of the most important criteria for making the diagnosis. It would appear that the Ivy bleeding time is a better screening test than the Duke bleeding time because the Ivy bleeding time is prolonged in situations in which the Duke bleeding time may be normal [1, 97]. The Duke method may be better for following therapy.

Many studies have been reported on the effect of blood and blood fractions on the bleeding time. The ability of blood transfusions to shorten the bleeding time was first reported by Geiger and Evans [42] in 1938. Schulman and colleagues [96] were able to correct the bleeding time by the transfusion of fresh-frozen plasma. The Duke bleeding time was shortened by the transfusion of a fraction (I-O of Blombäck) made from normal subjects as well as from patients with classic hemophilia [68]. The activity which caused correction of the bleeding time was distinct from fibrinogen, factor VIII, and platelets, and it was therefore suggested that the bleeding-time abnormality was due to the absence of "vascular factor." When the fraction was made from a patient with von Willebrand's disease, there was no effect on the abnormal bleeding time.

Although most workers have used the Duke bleeding time to evaluate blood [illegible]ons, the Ivy technique has been used and correction has been produced by hemophilic plasma, by a subfraction of Cohn fraction I precipitated by alcohol, and by cryoprecipitate. The method of preparing the fractions is extremely important, and Weiss [113] has shown that correction of the bleeding time is best produced when the fractions are made in siliconized apparatus.

In our experience, correction of the bleeding time (by either the Duke or Ivy technique) shows a great deal of variation. Nevertheless, although the bleeding time may not be decreased to within the normal range, visual inspection of the wound shows that the blood loss is decreased after therapy. Using the quantitative bleeding-time technique, we [106] have confirmed these observations and have shown that the amount of blood lost from the wound is strikingly decreased for a few hours after the transfusion of fresh-frozen plasma or cryoprecipitate.

Perkins [80] found that cryoprecipitate was able to correct the bleeding time. Therapy with cryoprecipitate is probably the treatment of choice for bleeding episodes and operations in these patients because it also induces the characteristic overresponse of factor VIII.

The correlation between the decrease of platelet adhesiveness found in von Willebrand's disease and the long bleeding time remains uncertain although it was supported by an international study [66] of the Salzman test. The association is an [illegible]us one because there is evidence that the absence of a plasmatic factor ac[illegible]s for the decrease of platelet retention in glass-bead filters in the same way that it has been postulated that the absence of a plasmatic factor accounts for the long bleeding time. The evidence for the existence of these factors needs to be strengthened, and it remains to be shown if they are one and the same.

Deficiencies of Coagulation Factors Other Than Factor VIII

It has been well established that there is a decrease of factor VIII activity in von Willebrand's disease, but there are many reports in the literature in which a long bleeding time has been associated with deficiency of factor I, V, VII, IX, X, or XI. The subject has been recently reviewed [15]. It is possible of course that the prolongation of the bleeding time in these patients may have been reduced by aspirin. It is interesting that many patients with labile factor (factor V) deficiency have greatly prolonged bleeding times [3, 41, 78].

In about one-third of the patients with congenital hypofibrinogenemia the bleeding time is prolonged [8, 9]. It is interesting to note that this observation was first made by Duke and later by Tocantins [110]. The long bleeding time in patients with hypofibrinogenemia may be explained by the rapid dissolution of platelet clumps which have been formed in the absence of fibrin [87]. In patients who have abnormal fibrinogens, the bleeding time is said to be normal [59].

Secondary Conditions

In Duke's original paper slight delays were reported in the onset of bleeding in the bleeding-time test on patients who were anemic, an observation confirmed by Hellem and colleagues [45], and it has been suggested than an adequate number of erythrocytes are necessary for normal hemostasis. In view of the tendency toward lower blood hemoglobin levels in women, it is interesting that O'Brien [70, 71] found that females at all ages tend to have a longer bleeding time.

The bleeding time may be prolonged in patients with intravascular coagulation and fibrinolysis but, with the multiple hemostatic defects including thrombocytopenia in many of these patients, it is difficult to identify one specific etiologic factor. Kowalski and colleagues [56], however, have shown that the larger fibrinolytic degradation products ("early FDP") caused prolongation of the bleeding time when injected into dogs but the smaller ones ("late FDP") had no effect. In these studies the bleeding time was measured by making two standardized incisions in the dog's ear. It appears that the degradation products interfere with platelet adhesiveness and aggregation and the effect of early FDP is more pronounced than that of late FDP.

Platelet abnormalities have been found in patients with renal insufficiency. They probably are the cause of the prolonged bleeding time which may be seen in these patients [54]. Prolongation of the bleeding time also has been reported in occasional patients who have liver disease and normal platelet counts [58].

COMMENT

In concluding this review of the various techniques and diagnostic applications of the bleeding-time test, in contemplating the noxious air which issued forth after the pricking of certain acupuncture sites, it seems to us that some of the literature on the bleeding time is not without a certain calorific gaseousness. In this extensive review we have not really answered the question "What does the bleeding time measure?" "The bleeding time measures the time of bleeding," said the Queen to Alice. Perhaps we should leave it at that, reflecting that we will continue to puncture the regions of Yin and Yang in performing the bleeding-time test because useful diagnostic information is produced, and we should always bear in mind that, for accuracy and reproducibility, the forces of Yin and Yang should be in balance, in the operator.

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